Strategy of Metal–Polymer Composite Stent To Accelerate Biodegradation of Iron-Based Biomaterials

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ABSTRACT: The new principle and technique to tune biodegradation rates of biomaterials is one of the keys to the development of regenerative medicine and next-generation biomaterials. Biodegradable stents are new-generation medical devices applied in percutaneous coronary intervention, etc. Recently, both corroding metals and degradable polymers have drawn much attention in biodegradable stents or scaffolds. It is, however, a dilemma to achieve good mechanical properties and appropriate degradation profiles. Herein, we put forward a metal–polymer composite strategy to achieve both. Iron stents exhibit excellent mechanical properties but low corrosion rate in vivo. We hypothesized that coating of biodegradable aliphatic polyester could accelerate iron corrosion due to the acidic degradation products, etc. To demonstrate the feasibility of this composite material technique, we first conducted in vitro experiments to affirm that iron sheet corroded faster when covered by polylactide (PLA) coating. Then, we fabricated three-dimensional metal–polymer stents (MPS) and implanted the novel stents in the abdominal aorta of New Zealand white rabbits, setting metal-based stents (MBS) as a control. A series of in vivo experiments were performed, including measurements of residual mass and radial strength of the stents, histological analysis, micro-computed tomography, and optical coherence tomography imaging at the implantation site. The results showed that MPS could totally corrode in some cases, whereas iron struts of MBS in all cases remained several months after implantation. Corrosion rates of MPS could be easily regulated by adjusting the composition of PLA coatings.

KEYWORDS: biodegradable polymer, surface coating, metal–polymer composite stent, cardiovascular repair, interventional treatment

1. INTRODUCTION

Biodegradable materials serve as one of the bases of regenerative medicine.1−3 Unfortunately, most of degradable materials do not exhibit some key properties like mechanical strength as good as those of well-known nondegradable materials. In theory, no material is absolutely stable, and the term “biodegradation” usually means that a material loses its ability of mechanical support or most of the mass within a certain medical treatment period, such as 3 years. So, to make a classic nondegradable or slow-biodegradable material “biodegradable” in the medically meaningful time scale is a very important fundamental topic in both material sciences and regenerative medicine. Herein, we report a case to use a facile material technique to make iron biodegradable by polymer coating during our effort in developing new-generation cardiovascular stents.

The advent of cardiovascular stents has opened a new era of the treatment of cardiovascular disease, with bare metal stents (BMS) as the first generation and drug-eluting stents (DES) as the second generation.6−11 For both BMS and DES, the presence of a permanent metal stent cages the vessel and interferes with future noninvasive imaging and treatment options.12 So, biodegradable or bioresorbable stents or scaffolds are much desired.13 For the third-generation stent, an ideal degradation time becomes a new key parameter. Extensive clinical experiments during the development of BMS and DES have revealed that an ideal cardiovascular stent should ensure sufficient initial scaffolding after implantation to eliminate vessel recoil and then it could lose most of mechanical support during a period, say, 3–6 months, to match tissue regeneration and be gradually absorbed by body to avoid long-term complications.7,14−16 The advantages of the classic stents,
especially good mechanical property, should be kept in the third generation. However, development of the new-generation stents has been faced with a bottleneck in finding appropriate biodegradable materials with both an ideal degradation profile and a sufficient initial mechanical support.

Corrodible metals and degradable polymers are two main categories of biomaterials to fabricate biodegradable stents or scaffolds. Many efforts have been made along these two technical lines, resulting in stents composed of polymers and metals. In general, metal stents exhibit better mechanical properties and polymers, especially polyesters, exhibit more adjustable biodegradation rates; both of the performances are extremely important for the third-generation stents. Of course, biocompatibility is another concern, especially when nonconventional materials are tried. So, using a composite technique based on conventional materials of quite different categories to generate new and useful functions is one of the strategies to accelerate the development of next-generation biomaterials.

As a conventional metal, iron exhibits better mechanical performance than most of polymers and metals. The pioneering work of iron stents was reported by Peuster et al. in 2001. They proved the feasibility and safety of iron stents by implanting the model stents in descending aorta of New Zealand white rabbits; most of iron remained after 18 month implantation, and there was no hint of biodegradation within 3 years. Since then, it has been well known that the low corrosion rate of iron has seriously limited its application as a biodegradable stent. So, iron stents have never been regarded as a mainstream biodegradable stent to be potentially commercialized during the last 16 years. Although the few in vivo studies on iron stents strengthen that iron is a suitable metal with no local or systemic toxicity in both short term and long term in different animal models, most reports point out that a higher corrosion rate is desired for corrodible iron stents. In the last decade, valuable efforts have been made to accelerate iron corrosion by alloying or surface modifications. Even though corrosion rates of iron have been increased to some extent, it is hard to achieve a total corrosion of iron stents in vivo.

Herein, we report a composite material technique to make iron stents biodegradable by polymer coating, which might shed new insight into biodegradable materials and afford a facile candidate technique for biodegradable cardiovascular stents. We develop metal–polymer stents (MPS) made up of iron-based struts and polyester coatings. In contrast, we suggest the term MBS (metal-based stent) to describe a bare iron stent. That is, to the best of our knowledge, the only reported strategy of biodegradable cardiovascular stents. We employ poly(lactic acid) (PLA), a popular biodegradable polymer to prepare the polyester coatings. In this report, the effect of PLA coatings on the corrosion behavior of iron sheets is demonstrated first by an immersion test in Hank’s solution mimicking plasma.

It seems worthy to point out that in vivo tests are much more important, as corrosion of iron is a complex process strongly depending on the corrosion microenvironment. So, by implanting the stents into artery vessel of rabbits, we then evaluated the corrosion behavior of the stents in the physiological environment directly. The corrosion profiles of MBS and MPS were assessed by implanting them in the abdominal aorta of New Zealand white rabbits. We measured residual mass and radial strength of the stents after implantation. Micro-computed tomography (Micro-CT) was used for a gross view of in vivo biodegradation of MPS versus MBS. Besides that, biocompatibility of MPS was examined by histological analysis and optical coherence tomography (OCT) imaging.

On the surface, a polymer coating might protect metal from corrosion, but we found that an appropriate PLA coating speeded up the iron corrosion eventually. The present study is aimed at reporting such an interesting phenomenon about applied materials and interfaces in vitro and in vivo.

2. MATERIALS AND METHODS

2.1. Preparation of Iron Sheet, MBS, and MPS. Iron sheets with thickness of 100 μm were cut into rectangles of size 26 mm × 22 mm and mechanically polished with SiC papers up to 2000 grits. The cut iron sheets were ultrasonically cleaned in acetone and anhydrous ethanol successively and then quickly dried by nitrogen gas. Granules of PLA (M₀, 60 kDa, Jinan Daigang Biomaterial Co., Ltd) were dissolved in ethyl acetate to prepare 1% w/v PLA solution. The PLA solution was then ultrasonically sprayed on the iron sheets for five times using an ultrasonic spray integration system (Ruidu Photo-electric, Shanghai, China). The syringe pump dispense rate of PLA solution was 0.10 mL/min, and the ultrasonic power was 4.75 W. A circular array of PLA coating was generated by covering a metal mask with regular arrays of circular holes (Φ2.0 mm) on iron sheet during the ultrasonic spraying process. Before the immersion test, the back side and peripheral edges of the PLA-coated iron sheets were sealed by silicone.

The metal-based stents (Φ3.0 × 8.0 mm²; weight, ~3.5 mg; iron strut thickness, 30 μm) were manufactured by Lifetech Scientific Co., Ltd. (Shenzhen, China) with laser cutting of iron tube. After being polished, the MBS were precisely weighed. MPS was prepared by spraying PLA solution on the MBS via ultrasonic spraying (Medicoat 4000, Sono-Tec). In detail, the MBS on a mandril was rotated into the atomizing PLA solution at a rate of 250 rpm. The ultrasonic power was 1.0 W, and the syringe pump dispense rate was 0.05 mL/min. Each MPS was weighed, and the mass of PLA coating was well controlled.

Three groups of MPS with different compositions of PLA coatings were prepared. They are MPS-A with 128 μg of PLA (M₀, 200 kDa), MPS-B with 128 μg of PLA (M₀, 200 kDa) and 32 μg of low-molecular-weight PLA (M₀, 50 kDa), and MPS-C with 160 μg of PLA (M₀, 200 kDa) and 32 μg of low-molecular-weight PLA (M₀, 50 kDa). For each MPS, 32 μg of rapamycin was loaded in the PLA coating. The rapamycin was dissolved in the ethyl acetate solution of PLA and sprayed on the stents along with the PLA. So, MPS here could also be called as iron-based drug-eluting coronary scaffold.

2.2. Characterization of Surface Wettability and Fourier Transform Infrared (FTIR) Spectroscopy of Bare Iron Sheet and PLA-Coated Iron Sheet. To inspect the surface wettability of iron and PLA-coated iron, 2 μL of Milli-Q water was dropped onto the surfaces automatically by a contact-angle-measuring device (JC2000DM, Zhongchen). The contact angles were calculated using the included software. For each sample, three measuring points were selected randomly and the results were averaged of three samples for each group.

We then employed FTIR spectroscopy to characterize the chemical groups on the surface. FTIR spectra of iron sheet and PLA-coated iron sheet were measured by Nicolet 6700 (Thermo Fisher). Each sample was placed on and directly contacted with an attenuated total reflectance crystal, and its FTIR spectrum was recorded between 4000 and 5000 cm⁻¹. Omnic 8.2 software was applied to analyze the spectra. The PLA film prepared by casting PLA solution into a glass dish was
introduced and deployed in the abdominal aorta under was introduced over a 0.014 in. guidewire. Then, the stents were accepted institutional policies and under the approval of the Ethics rabbits were used for in vivo corrosion tests. The rabbits were polished. cured for 8 h after Pt spraying. Then, the cross section was ground and the observation of the cross section of MPS under scanning electron microscope, MPS was embedded in resin (EpoxiCure, Buehler) and for the observation of the cross section of MPS under scanning electron microscope. MPS was embedded in resin (EpoxiCure, Buehler) and cured for 8 h after Pt spraying. Then, the cross section was ground and polished.

2.6. Implantation of Stents into Rabbits. New Zealand white rabbits were used for in vivo corrosion tests. The rabbits were purchased from Pearl Laboratory Animal Science & Technology Co., Ltd. The use of all experimental animals was in accordance with accepted institutional policies and under the approval of the Ethics Committee of the Shenzhen Testing Centre of Medical Devices. A total of 18 MBS, 9 MPS-A, 18 MPS-B, and 9 MPS-C were taken out from the abdominal aorta after 1, 3, and 6 months. In detail, segments of the rabbit abdominal aorta implanted with stents were cut and removed, and three stents of the same group were collected at each time point. After separating vascular tissues, the stents were immersed in ethyl acetate and ultrasonically cleaned for 20 min to thoroughly dissolve and remove the polymer coatings of the MPS. Corrosion products were then completely removed by ultrasonic cleaning using 3% tartaric acid. The mass of the remaining struts, namely, uncorroded iron struts, was weighed to determine the relative mass loss using an electronic balance with an accuracy of 0.001 mg (MES, Sartorius, Germany). Residual mass was calculated by dividing the mass of residual struts by the initial mass for MBS or by the initial mass of the iron struts for MPS.

2.7. Measurements of Residual Mass of Stents After Corrosion in Vivo. Animal experiments were conducted twice in the tests of stent residual mass. We examined the groups of MBS and MPS-A first. Because MPS-A was found without sufficiently higher degradation rate, we tried MPS-B and MPS-C further.

Initial masses of MBS and iron-based struts of MPS were measured before implanted in vivo. MBS and three kinds of MPS were taken out from the abdominal aorta of rabbits after 1, 3, and 6 months. In detail, segments of the rabbit abdominal aorta implanted with stents were cut and removed, and three stents of the same group were collected at each time point. After separating vascular tissues, the stents were immersed in ethyl acetate and ultrasonically cleaned for 20 min to thoroughly dissolve and remove the polymer coatings of the MPS. Corrosion products were then completely removed by ultrasonic cleaning using 3% tartaric acid. The mass of the remaining struts, namely, uncorroded iron struts, was weighed to determine the relative mass loss using an electronic balance with an accuracy of 0.001 mg (MES, Sartorius, Germany). Residual mass was calculated by dividing the mass of residual struts by the initial mass for MBS or by the initial mass of the iron struts for MPS.

2.8. Measurements of Radial Strength of Stents After Corrosion in Vivo. The segments of rabbit abdominal aorta scaffolded by MBS, MPS-B, or MPS-C were cut and moved out after 1, 3, and 6 months. Then, after removing attached adipose tissues, the radial stress of samples with minor surrounding vascular tissue was measured. Each sample was compressed in a radial strength tester (RX550-100, Machine Solution Inc.) at the compression rate of 0.1 mm/s, during which the outer diameter of the stents reduced from 4 to 2 mm.

The recorded stress at compression of 10% outer diameter of the original stents was set as radial strength with units of kPa. The radial strength at each experimental point was obtained by averaging the strength values of three stents. After the measurements of radial strength, the stents were used for residual mass test.

2.9. Histological Observations. The long-term biocompatibility and repair efficacy were also preliminarily examined. The abdominal aorta segments scaffolded by MPS-B were taken out after 12 month implantation. The hard tissue slices of the scaffolded vessel segments were prepared by embedding with poly(methyl methacrylate) resin, slice sectioning (IsoMet 5000, Buehler), and staining with hematoxylin and eosin (HE). The femoral artery was surgically exposed, and a SF guide catheter was introduced over a 0.014 in. guidewire. Then, the stents were introduced and deployed in the abdominal aorta under fluoroscopic control. Balloons were inflated with 8–10 atm for 30 s to deploy the stents. The rabbits were fed with a standard diet without cholesterol or lipid supplementation throughout the experiments.

2.10. Micro-CT Imaging of Stents Taken from Rabbits. Segments scaffolded by MBS and MPS-B were dissected from the rabbit abdominal aorta after 3 and 12 month implantation. The segments were observed by micro-CT (Skyscan1172, Bruker, Germany) with a resolution of 0.5 μm. Gross structures of the two kinds of stents were observed using Al filter.

2.11. OCT Imaging in Living Animals. OCT imaging was performed at the baseline and 12 month follow-up with C7 XR Fourier-Domain System (LightLab Imaging, Westford, MA). A conventional wire was placed distally to the segments of interest; the OCT catheter (RX ImageWire II, LightLab Imaging, Westford, MA) was advanced distally to the target region. Removal of the conventional wire was left to the operator’s discretion. The pullback was performed...
during a continuous injection of contrast medium (Iodixanol 370, Visipaque, GE Health Care, Cork, Ireland) at a rate of 4 mL/s through the guiding catheter. In this case, the fiber was withdrawn at a speed of 20 mm/s and the OCT images were generated at a rate of 100 frame/s. The resolution of the OCT system is 15−20 μm in both lateral and axial directions.

3. RESULTS

3.1. In Vitro Immersion Tests of Iron Sheets with and without PLA Coating. To demonstrate the acceleration of iron corrosion by PLA, we prepared a PLA array on an iron sheet, as illustrated in Figure 1A. While the back side and peripheral edges of each sample were well sealed, the upper surface contacted with Hank’s solution, which has the same inorganic salts as plasma. The transparent PLA coating was invisible under macrography and optical photography.

After immersed in Hank’s solution for 2 days, the areas covered by the PLA array corroded noticeably, and brick-red rusts were accumulated, as shown in Figure 1B. In contrast, there was no sign of corrosion at the surface of bare iron. So, it was the PLA coating that accelerated iron corrosion. On day 4, the whole iron sheet corroded on the surface.

Generally speaking, a polymer coating hinders metal corrosion. In this experiment, although iron corrosion might be blocked by PLA coating at the very early stage, it started to be accelerated after a certain time (less than 2 days under the present experimental conditions). It seems worthy of noting that iron corrosion in a coating array might not be identical to that under a homogeneous coating in light of electrochemistry. Nevertheless, iron under a complete PLA coating also presented a higher corrosion rate after a few days. As shown in Figure S1, although just a few corrosion sites appeared on bare iron sheet after 2 days, numerous corrosion sites were observed on the PLA-coated iron. So, our in vitro immersion tests certified that the PLA coating can eventually accelerate the iron corrosion.

3.2. Surface Wettability and FTIR Spectroscopy of Bare Iron and PLA-Coated Iron. We employed water contact angles to characterize the surface wettability of bare iron sheet and PLA-coated iron sheet. The results in Figure 2A indicated that the surface of the PLA coating was more hydrophobic than that of bare iron.

We also used FTIR spectroscopy to detect the surface chemistry. The absorption peaks of the PLA-coated iron in the FTIR spectrum were consistent with those of the PLA film, as displayed in Figure 2B, which illustrated that the PLA coating was formed on the iron sheet successfully.

3.3. In Vitro Cytotoxicity. We conducted extraction experiments to examine cytotoxicity of the new biomaterial system according to ISO 10993-5-2009 (E) and ISO 10993-12-2007 (E). The cytotoxicity of the extraction culture medium of bare iron and PLA-coated iron was evaluated quantitatively by CCK-8. Little cytotoxicity was detected for extraction of both bare iron and PLA-coated iron, as displayed in Figure 3. The cell viability of the extraction medium for the PLA-coated iron was as high as 90%, close to that for cell culture plate (100%) and higher than 80%, which is thought to be of only a little cytotoxicity.

So, the PLA-coated iron was proved to have a higher corrosion rate and better cytocompatibility than the bare iron according to our in vitro experiments of two-dimensional sheets. To investigate the effects in vivo and explore the potential clinical applications in the future, we fabricated three-dimensional stents with PLA coatings in the following experiments.

3.4. Morphology of MPS and PLA Coating. The MPS with an obvious metallic luster was obtained after laser cutting, polishing, and ultrasonic spray coating. As shown in Figure 4, the as-prepared metal strut was of a smooth surface and covered by a uniform PLA coating. The average thicknesses of PLA coatings of MPS-A, MPS-B, and MPS-C were about 6.5, 8.5, and 10 μm, respectively, due to different amounts of the polyester. The strut thickness of MPS was less than 70 μm (about 50 μm for the iron strut), which is even thinner than...
clinically used XIENCE V Everolimus-eluting cobalt chromium stent very famous for its thin strut (81 μm).

3.5. In Vivo Corrosion Rates of Stents. The parameters of polymer coatings were found to influence corrosion rates significantly. In the animal experiments, we examined three groups of MPS with coatings of different amounts of the biodegradable polymer PLA or different ratios of PLA with high and low molecular weights. All of the stents were implanted in

Figure 4. Morphology of MPS as prepared. Gross view of MPS mounting on the balloon catheter (left), SEM image of a local stent (middle), and cross section of the strut (right).

Figure 5. In vivo corrosion profiles in terms of residual mass of the stents. Stented segments were dissected from rabbit abdominal aorta 1, 3, and 6 months after implantation, and residual mass was expressed as a percentage of the uncorroded iron struts at each time point. (A) MPS-A vs MBS. (B) MPS-B and MPS-C vs MBS. Means and standard deviations from three independent groups are presented. A and B come from two rounds of experiments and thus even the data for the control group of MBS are not identical to each other.

Figure 6. In vivo corrosion profiles in terms of radial strength of the stents. (A) Radial stress as a function of outer diameter of a stent in the radial compression experiment, with the stress at 10% compression of the original stents defined as radial strength. (B) Radial strength of indicated stents after implanted in abdominal aorta of rabbits for 1, 3, and 6 months. “NA” in the cases of MPS-B and MPS-C in month 6 represents that stents corroded so severely that measurements of the radial strength were not available.
the predetermined segments of the abdominal aorta in 18 rabbits without any complications (three stents in per rabbit). Angiography after the implantation of the stents showed that the abdominal aorta was of patency in all animals with no signs of intraluminal defects or dissection of the vessel wall.

Gravimetric determination from periodic sampling of explant weight is the main method in tracking the degradation process of a biodegradable material. Using this method, we monitored the residual mass of MBS and MPS-A after the implantation, with results shown in Figure 5A. The residual iron of MBS decreased slowly, and 73.3 ± 4.1% of iron struts still remained 6 months after the implantation. In contrast, the PLA coatings of MPS-A accelerated the corrosion of iron stents in the first month.

As the acceleration of iron corrosion might be attributed to the relatively lower local pH produced by PLA hydrolysis, we thought that increasing the amount of PLA or adding low-molecular-weight PLA might make a longer and stronger effect of PLA coating on the iron corrosion. So, MPS-B and MPS-C were prepared to accelerate the corrosion of iron stents. As presented in Figure 5B, residual mass dropped dramatically over time in 6 months for MPS-B. As there is 32 μg more PLA ($M_w$, 200 kDa) of MPS-C coating than MPS-B, the residual mass of MPS-C dropped even more rapidly. With increasing the total amount of PLA and adding low-molecular-weight PLA in the coating, MPS-B and MPS-C corroded faster than MPS-A, and a complete corrosion of iron struts was successfully achieved in 3–6 months in vivo.

The two rounds of in vivo experiments confirmed that corrosion of iron stents could be accelerated by PLA coatings. Our experiments also indicated that the corrosion rate can be easily adjusted by the PLA coatings, which is quite important for biodegradable stents.

Radial force of stents is an essential factor to prevent recoiling and achieve constrictive remodeling of the vessel at the initial stage. A biodegradable stent is desired to guarantee scaffolding the vessel in the first 3 or 6 months after implantation. MBS, MPS-B, and MPS-C were examined after implantation for 1, 3, and 6 months. A typical curve of radial stress versus outer diameter of stent is shown in Figure 6A. According to the standard radial compression experiment, the stress at 10% compression of the original stent was defined as the radial strength.

The resultant radial strengths of the periodical explants are shown in Figure 6B. After 6 months, the MPS-B and MPS-C corroded so seriously that the compression experiment could not be conducted. These results indicate that MPS can scaffold the vessel during the first 3 months and free the caged vessel after 6 month implantation.

So far, we have investigated residual mass and radial strength to quantitatively track the corrosion profiles of MBS and MPS after implantation for 1, 3, and 6 months. Compared to MBS,
corrosions of all of the three groups of MPS were accelerated. Considering the time dependence of residual mass and radial strength in Figures 5 and 6, we chose MPS-B of an intermediate degradation rate to undergo further long-time follow-up experiments.

3.6. Observation of Stents Using Micro-CT. It is not possible to track the corrosion process of MPS-B in terms of residual mass and radial strength 6 months or longer after implantation because the iron stents have corrupted and the two above tests of separated residual stents after removing surrounding tissues and corrosion products are then not available. So, we employed micro-CT to straightforwardly visualize the longer-term corrosion morphology of the stents through surrounded tissues.

Stents were clearly observed under the micro-CT with the high resolution of 0.5 μm. As shown in Figure 7, MPS corroded more severely than MBS both in the 3rd and 12th month. Although most of the iron struts of MBS still did not corrode in the 12th month, the MPS almost totally corroded. The micro-CT imaging strengthened that PLA coatings could accelerate iron corrosion. It can also be seen that the corrosion products were mainly located in situ.

3.7. Histological Observation. We also made preliminary examination of the long-term biocompatibility of the implanted stents. As a demonstration, an HE staining image is presented in Figure 8. The cross section of rabbit’s abdominal aorta scaffolded by an MPS-B after 12 month implantation. HE staining was made prior to the observation.

Figure 8. Optical micrograph of the cross section of a rabbit abdominal aorta scaffolded by an MPS-B after 12 month implantation. HE staining was made prior to the observation.

A new material system in MPS does not lead to significant biocompatibility problems.

3.8. OCT Imaging in Living Animals. While all of the above observations or measurements were eventually made in vitro or ex vivo, we also used OCT to observe the implanted site in a living animal. OCT is a powerful tool for stent assessment and has got to be the modality of choice for studies of stents and vascular interactions. In OCT detection, near-infrared light is used to capture micrometer-resolution three-dimensional images within an optically scattering biological tissue. Herein, OCT was applied to follow the corrosion and biosafety of MPS-B in vivo. Strut appearance of MPS-B was investigated at both baseline and 12 month follow-up, as shown in Figure 9.

At baseline, the OCT image of the scaffolded segment indicated that the strut struts attached well to the vessel wall. Neither strut struts malposition nor thrombus was found, which illustrated a good compliance and hemocompatibility of MPS-B. A great deal of the OCT light energy was reflected at endoluminal sides of the MPS-B struts, which generated a visible optical border and shadow behind the struts.

At 12 month follow-up, the struts could hardly be identified. The obscure and disperse shadows of struts reflected a loose structure of corrosion products (Figure 9), which is consistent with our micro-CT observations (Figure 7). It is satisfactory that after 12 month implantation, the strut struts were totally covered by neointima and thus new tissue was regenerated using the biodegradable composite stent as a scaffold.

4. DISCUSSION

A metal–polymer composite strategy was suggested to accelerate iron corrosion by coating of biodegradable polyester. It is very interesting that a polymer coating did not hinder iron corrosion except the very early stage, but accelerated iron corrosion eventually, as demonstrated in the in vitro immersion test of iron sheets with and without PLA coatings (Figures 1 and S1). Such an effect was further confirmed by implanting three-dimensional stents in the abdominal aorta of rabbits. The in vivo corrosion behaviors (Figures 5 and 6) verified that the MPS technique enabled the total loss of the iron mass and stent strength within 6 months and that the degradation rates could be adjusted by tuning parameters of polymer coatings. The results of residual mass and radial strength as a function of degradation time (Figures 5 and 6) along with the micro-CT observation (Figure 7) indicated a faster corrosion of MPS than MBS.

4.1. PLA Coating Can Accelerate Iron Corrosion by Altering Local pH. Arterial blood is a weak alkaline (pH 7.4) and oxygen-rich (13.3 kPa) aqueous medium. MBS contacted with the blood or nearby tissue fluid and were thus under a weak alkaline environment. In contrast, MPS might be in a relatively lower pH environment due to PLA hydrolysis. So, the acceleration of iron corrosion by the PLA coating could be attributed to the decrease of the local pH adjacent to iron surface. Early in 1924, three scientists from MIT have concluded that the decrease of pH accelerated metal corrosion when they examined the effect of hydrogen-ion concentration on the submerged corrosion of steel. So, our experimental results of iron corrosion are well consistent with the previous report of steel corrosion in principle.

4.2. Corrosion Rate of MPS Can Be Tuned by the Amount and Molecular Weight of PLA in the Polymer Layer. A higher corrosion rate of MPS than MBS was achieved by PLA coatings, which was attributed to the effect of the PLA.
coating and its degradation products. So, the corrosion rate of MPS was adjusted by tuning PLA parameters, as shown in Figure 5. By adding lower-molecular-weight PLA or increasing the amount of PLA, a faster corrosion was achieved from MPS-B versus MPS-A and from MPS-C versus MPS-B.

PLA degrades via hydrolysis of ester bond into two segments: one segment with a new carboxylate end and another segment with a new hydroxyl end. Because carboxylate is a catalyst of the later ester hydrolysis, biodegradation of the PLA bulk exhibits autocatalysis. So, PLA of lower molecular weight degrades faster than that of higher molecular weight and thus more water-soluble oligomers and lactic acids could be generated over the same period time for PLA of lower molecular weight.50 The oligomers and monomers could enhance the degradation of PLA further, which results in more polymer chains and terminal carboxyl groups.51 Of course, an increase in the amount of PLA of the same molecular weight can also increase the polymer chains and terminal carboxyl groups. So, the corrosion rate of MPS can be increased both by adding lower-molecular-weight PLA and by increasing the amount of PLA.

A small amount of PLA in the coating layer can lead to an accelerated corrosion of MPS just at the early stage. That is why MPS-A showed more rapid corrosion than MBS only in the first month, as presented in Figure 5A. By adjusting the composition of PLA coatings, a continuous acceleration of corrosion of MPS can be achieved, as demonstrated in MPS-B and MPS-C in Figure 5B and also in Figure 6. Considering the balance of corrosion rate and scaffolding time of MPS, the proportion of PLA and iron struts should be in good match.

4.3. Biosafety of MPS: The Amount of Iron Element Introduced into the Body by MPS is Acceptable. As a new biomaterial system, we should, of course, care the biocompatibility and biosafety of MPS. Here, attention shall be paid to the issues related to degradation products of the MPS. An excessive intake of metallic elements might cause biosafety problems, but we eliminate such a worry after rational analysis of MPS.

Iron is an essential element in human body and plays important physiological functions. The amount of Fe in healthy adult is about 4−5 g, 65% of which exists in hemoglobin for participating in oxygen transport.52 For a healthy adult, 1−2 mg of iron should be absorbed from diet per day.53 The excellent mechanical properties of iron allow a thin strut thickness of MPS, which results in a less amount of iron applied in each stent. A stent in our experiments weighed 3.5 mg, which is less than 3.5 days of iron intake for an adult. Because the stents degraded over a few months, the concentration of iron would be negligible in comparison to the physiologic plasma iron content.

4.4. No Hydrogen Bubble from MPS under Physiological Condition. Another important issue related to biosafety of metal corrosion is the hydrogen bubbles probably generated during hydrogen evolution. Actually, during our 12
month follow-up, no hydrogen bubbles or gas pockets in tissue were observed in the in vivo imaging detection.

As the stents are close to a weak alkaline blood or tissue medium (pH 7.4) and the corrosion of iron can produce an alkaline environment, some H⁺ may be consumed quickly. Although the PLA hydrolysis must lead to a relatively lower local pH, the net result of the local pH on the iron surface might be only near-neutral. So, it is understandable that no hydrogen bubble was observed in our experiments of composite stents.

4.5. Other Issues about Biocompatibility and Effectiveness of MPS. In this study, the cell viability under an extract medium was examined, and the in vitro experiments of HUVECs indicated less cytotoxicity of the PLA-coated iron, as shown in Figure 3.

The biocompatibility of MPS was also straightforwardly estimated by implanting the stents in the abdominal aorta of rabbits. Histopathological evaluation of MPS 12 months after implantation (Figure 8) showed that insoluble corrosion products were completely covered by neointima. No remarkable neointimal proliferation and inflammatory response was observed.

At the baseline of OCT imaging (Figure 9), no strut malapposition or strut thrombus was found. Besides, all animals survived the 12 month follow-up period without any adverse clinical events. In brief, MPS showed good biocompatibility and biosafety in the abdominal aorta of rabbits. And eventually, the stent struts were totally covered by neointima.

MPS is a combination of iron and polyester, which are two representative materials in corrovable metals and degradable polymers, respectively. Biocompatibility of iron-based materials has been studied both in vitro and in vivo in the last decade. Ferrous ions, a possible product during iron corrosion, were proved to enhance the viability of endothelial cells in lower concentration (<10 μg/mL). Results of in vivo experiments all showed that iron-based stents and its corrosion products had no local or systemic toxicity in both short term and long term.

Our previous work also demonstrated long-term biosafety of the insoluble iron corrosion products of MBS, which were cleared away by macrophages from in situ 53 months after implantation in the porcine models.

PLA and other aliphatic polyesters have been widely used in tissue engineering and regenerative medicine. Their hydrolysis products can be finally metabolized to CO₂ and H₂O. Absorbable stents made of PLA has been approved by the Food and Drug Administration for application in the treatment of coronary stenosis. As both iron and PLA have good biocompatibility, the MPS made up of the two materials are supposed to have good biosafety as the new generation of biodegradable coronary stents for tissue regeneration.

A thinner stent strut means broader applications in blood vessels of various sizes and better adaptability in the noninvasive interventional treatment. As iron has better mechanical performance than most of polymers and corrovable metals, a thinner iron strut is sufficient to maintain necessary radial strength to scaffold the vessel at the initial stage.

After we submitted the manuscript, a paper about biodegradable stents using a composite strategy was published online. In such a stimulating publication titled “[T]he development of bioersorbable composite polymeric implants with high mechanical strength”, they reported a polymer–polymer composite stent using one polymer coating on another polymer to enhance the mechanical properties of the resultant stent. In contrast, our present work put forward a metal–polymer composite strategy mainly to enhance the biodegradation rates of the iron-based biomaterials. So, the academic and industry fields have at least two alternative composite systems to fabricate stents, both with appropriate mechanical properties and biodegradation rates. Further studies on the function of our composite stent of MPS and the mechanism of the iron corrosion accelerated by PLA coatings will be discussed in the following work.

5. CONCLUSIONS

A strategy employing facile polyester coating has been suggested and verified to make iron stents biodegradable (actually corrovable in the clinically required time scale), which is otherwise of very low corrosion rate in vivo. A complete loss of strength of iron stents was achieved in 3–6 months in vivo by appropriate PLA coatings. The faster corrosion of MPS than MBS might mainly be attributed to the effects of degradation products of PLA hydrolysis. Tissue regeneration was observed in animal experiments by implanting stents into the abdominal aorta of New Zealand white rabbits. With proper composition of PLA coatings, MPS is a candidate of the biodegradable coronary stents.

The present study demonstrates that two of the main categories of biomaterials, corrovable metals with good initial mechanical strength and degradable polymers with easily tunable degradation rate, can be combined to fabricate composite biomaterials of both satisfactory mechanical properties and desired biodegradation profiles. Such a new principle seems useful for R & D of biomaterials and regenerative medicine and might be stimulating also for some other applied materials concerning polymers and metals if degradation or corrosion rates should be tuned or cared significantly.

■ ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsami.7b15206.

Supporting experiments to demonstrate that a PLA coating can accelerate iron corrosion in vitro (PDF)

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■ ACKNOWLEDGMENTS

This work was financially supported by the National Key R&D Program of China (Grant No. 2016YFC1100300) and the National Science Foundation of China (Grants Nos. 51533002 and 21604011).
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